REMARKS

Applicant respectfully requests reconsideration. Claims 28-34 and 36 were previously pending in this application. No claims are amended herein. As a result, claims 28-34 and 36 are still pending for examination with claims 28 and 29 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 103

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al. 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al., 1990 The American Chemical Society, Vol. 1, No. 3 pgs 165-182, Hutcherson et al. U.S. Patent 5,723,335 March 3, 1998 (filed March 25, 1994).

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al. 1992 Jpn. J. Cancer Res. Vol. 83 pgs. 244-247 in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al., U.S. Patent 5,723,335 March 3, 1009 (filed March 25, 1994), and Cheng et al., U.S. Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994).

Applicant previously argued that the skilled artisan would not have modified the ODN of Kuramoto et al and Kataoka et al by adding phosphorothioate internucleotide linkages because of the unpredictability of phosphorothioate linkages. The Examiner has dismissed Applicant's arguments and asserted that it was known in the art that phosphorothioate backbones should be used with immunostimulatory oligonucleotides and that a change in backbone would affect the properties of the immunostimulatory oligonucleotides. Two references were cited by the Examiner, Agrawal et al and Hutcherson et al. Applicants disagree with the Examiner's conclusion. Additionally the references previously cited by Applicant have not been addressed.

The skilled artisan at the time of the invention would not have combined the teachings of Kuramoto et al or Kataoka et al with Goodchild or Hutcherson to produce the ODN of Kuramoto et al or Kataoka et al having phosphorothioate internucleotide linkages for reasons provided in more

detail below. It is only in hindsight, using Applicant's disclosure would the skilled artisan have been motivated to make such a combination.

The skilled artisan at the time of the invention would not have combined the teachings of Kuramoto et al or Kataoka et al with Goodchild to produce a phosphorothioate modified ODN because of the unpredictability of phosphorothioate backbone modifications. At the time of the invention it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides. It was not clear how a change in backbone would affect the properties of phosphodiester based immunostimulatory oligonucleotides. Applicant previously cited several papers as evidence that it was unpredictable.

In response to Applicant's arguments the Examiner cited Agrawal and Hutcherson as support that the skilled artisan would have used phosphorothioate linkages in immunostimulatory ODN. It is stated in the Office Action (pages 9-10) that Agrawal teaches that phosphorothioate backbones "should be used with immunostimulatory oligonucleotides". Applicant is not aware of such a teaching in Agrawal et al. Agrawal et al (US Patent No. 5194428) describes antisense ODN for treating influenza virus infection. In particular it is taught that the antisense ODN "have antiviral activity against influenza virus as a result of their ability to hybridize to a selected region of influenza virus RNA and inhibit its ability to serve as a template for synthesis of encoded products". (Abstract). Antisense is a different mechanism of action than immune stimulation. Agrawal does not provide a teaching to the skilled artisan that phosphorothioate backbones should be added to immunostimulatory ODN.

It is further stated in the Office Action that Hutcherson et al teach that phosphorothioate ODN analogs enhance immune stimulation. However, the skilled artisan would not have modified the ODN of Kuramoto et al or Kataoka et al to add phosphorothioate linkages based on the teachings of Hutcherson because the teachings of the two references are inconsistent and further in view of the known unpredictability of the phosphorothioates in the art, as discussed below. Kuramoto et al and Kataoka et al teach that the immunostimulatory DNA is representative of immunostimulatory bacterial DNA. Bacterial DNA is not phosphorothioate modified. Kuramoto et al and Kataoka et al further teach that the immunostimulatory activity of the ODN is due to the hexameric palindrome within the sequence. Hutcherson describes generally that phosphorothioate

ODN analogs can provoke an immune stimulatory response. However, Hutcherson does not provide any teaching regarding inclusion of a palindrome. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity. The skilled artisan attempting to create a synthetic version of bacterial DNA that was immunostimulatory would not have been motivated to phosphorothioate modify it because of the teachings of Hutcherson. Hutcherson is describing molecules that are distinct from Kuramoto et al and Kataoka et al in that they are phosphorothioate modified and are sequence independent.

The skilled artisan would have expected that the molecules of Kuramoto et al/Kataoka et al and Hutcherson were operating through different mechanisms. Without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids. In the absence of the work of the instant invention it would not have been known at the time of the invention whether a phosphorothioate bond or phosphorodithioate bond would substantially change the shape of the oligonucleotide so as to totally destroy immunostimulatory ability.

Further, Applicants presented evidence of the unpredictability of phosphorothioate linkages. As none of that evidence has been addressed, Applicant reiterates those arguments. A 1993 *Science* paper by Stein et al (Science v. 261 p. 1004 1993) shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation *in vivo*. As detailed in Stein et al those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction.

Phosphate backbone modifications were known to have unpredictable effects on nucleic acids. Among the complications introduced by phosphorothioate modification is the creation of

stereochemistry. The sulfur in a phosphorothioate modification introduces stereochemistry at each bond where it is present, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. Because stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties. This stereochemistry of phosphorothioates was known prior to 1994. One of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation. This stereochemistry does not occur with the usual oxygen. In addition to the stereochemistry, the sulfur atom can have further effects on the activity of the nucleic acid simply due to its being much larger than the oxygen.

Thus, in view of the different teachings between Kuramoto et al/Kataoka et al and Hutcherson et al and the expected different mechanisms of action as well as the unpredictability of phosphorothioate bonds the skilled artisan would not have combined the teachings in the absence of hindsight.

Double Patenting Rejection

Claims 28 and 36 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122 and 124 of co-pending Application No. 10/314,578. Applicants arguments have been dismissed because according to the Examiner US 7271156 shares a common inventor with the present application. Applicant disagrees.

As far as Applicant is aware, neither the case law nor the MPEP states that two patent applications which are not commonly owned (identical ownership) and which don't have identical inventorship are subject to obviousness type double patenting. Application of double patenting in a circumstance when the patents are not commonly owned and do not have identical inventorship and the claims under rejection have the earliest effective priority date would be contrary to the public policy reason for double patenting. The public policy behind the double patenting doctrine is to allow the public to freely use a patent upon its expiration an to prevent an entity from obtaining

multiple patents on one invention including obvious variations. "The basic concept of double patenting is that the same invention cannot be patented more than once, which, if it happened, would result in a second patent which would expire some time after the original patent and extend the protection time wise." *General Foods Corp. v. Studiengesellschaft Kohle MbH*, (972 F.2d 1272, 1279, 23 USPQ2d 1839, 1844 (Fed. Cir.. 1992)). (See also *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) and MPEP 804B). The judicially created doctrine of obviousness type double patenting was originally implemented to prevent issuance of two patents that otherwise did not qualify as prior art against one another. The instant application is prior art under 35 USC 102(e) against US 7271156. US 7271156 which has an earliest effective priority date of September 25, 1999 is not prior art under any other section of the statute against the instant applicants or any other party that filed a patent application prior to 1999. Further, issuance of the instant patent application would not extend the patent protection beyond a point by which the public would otherwise be free to use the technology. To apply a double patenting rejection in the instant circumstance would extend beyond the purpose of the nonstatutory obviousness-type double patenting. Thus, double patenting is not appropriate in the instant circumstance.

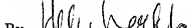
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US07.

Dated: January 12, 2009

Respectfully submitted,

By 

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